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The problem of the use of drugs in pregnant women and the role of pharmaceutical care in preventing the unwanted effect of drugs on the fetus

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Abstracts

The article reviews the peculiarities of women's drug utilization during pregnancy. The external and internal negative factors that affect the development of the fetus are discussed, the types of their undesirable effects (embryotoxic, teratogenic, fetotoxic, etc.) are presented, the possible mechanisms of toxic effects are indicated, and the critical periods of the child's development are described. Emphasis is placed on the approaches and rules of the pharmaceutical care of a pregnant woman by a pharmacist during her responsible self-medication. *(Farm Współ 2022; 15: 143-150) doi: 10.53139/FW.20221522*

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A modern pharmacist's primary and the most important functions are to provide the population with high-quality medicines and medical products, monitor their use's effectiveness and safety, provide qualified advisory assistance and conduct pharmaceutical care [1,2]. Among the pharmacy customers today, particular groups of patients need close attention due to their age, unique physiological state, concomitant disease (especially chronic), and other features. Thus, the category of special patients includes:

- pregnant women,
- lactating and breastfeeding women,
- children (between the developmental period of infancy and puberty),
- persons with chronic diseases,
- middle-aged persons, elderly, long-lived elderly.

Sometimes patients with infectious diseases, tourists or patients who have moved from other countries and have different linguistic and cultural characteristics are defined as special groups, too [3]. Each of these groups has its own peculiarities of patient communication, medicine and dosage form choice, proper intake consulting, and adverse drug reaction monitoring.

Pregnant women are an exclusive group, because in addition to purely medical and pharmacological questions, the ethical ones are added. Taking the medicines the future mother exposes to the risk of unwanted effects not only her body, but also another life, which is vulnerable, defenseless and very sensitive to any external influence. The rational choice of a drug for a pregnant woman is an intricate problem because of the lack of reliable clinical data due to ethical obstacles to conducting clinical studies on the medicine's effect on the body of a pregnant woman and her child [4,5].

In principle, pregnancy is a natural, physiological state for a woman and does not require the use of medicines. However, according to the research data, about 80-90% of pregnant women use drugs. In some researchers' references, this level increases to 99% [6,7]. Also, scientists have shown that pregnant women use at least one of the prescription drugs represented by all 15 basic groups according to the ATC (The Anatomical Therapeutic Chemical) classification at 90 days before pregnancy, during pregnancy and 90 days after childbirth [8,9].

The most common reasons for prescribing drugs are:

- prevention of chronic disease exacerbations and complication treatment (diabetes, rheumatoid arthritis, bronchial asthma, thyroid hormone metabolism disorders, etc.);
- acute infectious disease treatment (bronchitis, pneumonia, urinary system infections);

- correction of pregnancy complications (hypertension, gestational diabetes, preeclampsia, anemia, etc.);
- prevention and repletion of biologically active substance deficiency (vitamins, micronutrients);
- prevention and treatment of fetal pathology through the mother's body (use of corticosteroids in case of insufficient lung development in the fetus) [10-16].

It should be noted that this list does not include common minor disorders that pregnant women can eliminate without consulting a doctor but by self-medication:

- different types of pain (headache, joint pain, toothache),
- functional gastrointestinal disorders (heartburn, constipation),
- light signs of cold (sore throat, runny nose, cough),
- allergy symptoms (urticaria),
- insomnia, anxiety, etc. [17].

Thus, the list of conditions, as well as the list of drugs that a pregnant woman can potentially use, is significantly expanded and supplemented by over-the-counter (OTC) drugs, the independent purchase and intake of which are difficult to control.

A study conducted in European, North and South American and Australian countries has shown that 81.2% of pregnant women used at least one drug, 66.9% of which were OTC drugs. Moreover, 68.4% of pregnant women used them to treat acute/short-term illnesses, and 17% for chronic/long-term disorders [18]. For example, in 2013-2018, a French study focused on pregnant women's consumption of drugs affecting the gastrointestinal tract showed that 74% of women took at least one drug from this group. The distribution by pharmacological groups revealed that a significant part of the group consists of OTC drugs – about 1/3 of pregnant women took antacids (37%) and antinauseants (31%), while 10.3% used antidiarrheals, and 15.3% laxatives [9].

According to the published data, the use of drugs by a pregnant woman can lead to spontaneous abortions, premature births and fetus hypotrophy. When mothers use medicines during pregnancy, the risk of perinatal allergy in children increases [19-22]. Among the types of unwanted effects of drugs during pregnancy, the following can be distinguished:

1. Embryo-lethal (pre- and post-implantation death of the embryo).
2. Embryotoxic (functional and structural disorders of the embryo cell systems, which violate the implantation and placentation processes).
3. Teratogenic (developmental abnormalities, malformations).
4. Fetotoxic (functional and structural disorders of fetal cell systems, for example, magnesium sulfate, used for tocolytic purposes, due to suppression of the fetal CNS, can cause muscle weakness, impaired breathing and sucking in a newborn).
5. Mutagenic (structural changes in DNA in germ and somatic cells).

However, globally, adverse effects of drugs during pregnancy can be separated into two categories, teratogenic or foetotoxic. A teratogenic drug is defined as causing irreversible impairment to the newborn, affecting the organs during embryological development and thus causing birth defects. It often leads to the death of a newborn in the first hours/days. A fetotoxic drug is a drug that has a detrimental effect on foetal growth and organ function [23]. These effects can be due to the dose, the duration of exposure, the route of administration, the concomitant exposures, the period of exposure during pregnancy and potential genetic predispositions.

The list of teratogenic factors, in addition to drugs, includes:

- *Infections* (rubella, herpes, cytomegalovirus, herpes simplex virus, human immunodeficiency virus, chicken pox virus).
- *Ionizing* radiation, which causes the death of rapidly proliferating cells when exposed to the teratogen. Radiation is also a mutagen, responsible for genetic changes in germ cells and the subsequent development of birth defects.
- *Chemical* factors, including drugs.
- *Maternal* diseases, in particular diabetes [24].

Undoubtedly, the most critical task for a doctor and a pharmacist/clinical pharmacist is detecting risk and preventing drug-induced teratogenic or fetotoxic effects.

Sensitivity to teratogenesis, the risk of development, and the nature and severity of the fetus's negative effect manifestation are determined by factors that, concerning drugs, coincide with those for side effects and are divided into the active pharmaceutical ingredient (API) property-depending and the individual organism-depending (table I):

1. The embryo genotype and the ways of interaction of this genetic material with the external environment. The mother's genome is an essential factor in drug metabolism, resistance to infections, and other biochemical and molecular processes that affect the embryo.
2. Stage of fetal development at the time of teratogen action (see below).
3. Dependence of the severity of manifestations of abnormal development on the dose and duration of action of the teratogen (dose-dependent effect).
4. The specificity of teratogen action on developing cells and tissues. These mechanisms of pathogenesis include the inhibition of biochemical and molecular reactions, cell death, reduction of cell proliferation and other phenomena [25-27].

Table I. Factors of teratogenesis specificity

Peculiarities of teratogen — active pharmaceutical ingredient	Peculiarities of an individual organism
1. API dose 2. Duration of API exposure 3. Way of API administration 4. Physical and chemical properties of API	1. Chronic diseases 2. Pregnancy stage 3. Potential genetic predisposition

API (Active Pharmaceutical Ingredient) physical and chemical properties determine the ability and speed of API passage through the placenta and the nature of distribution in fetal tissues, amniotic fluid and other pharmacokinetic features [28]. Maternal and fetal drug concentrations depend on the amount of drug that crosses the placenta, the extent of metabolism by the placenta, and fetal distribution and drug elimination. Diffusion across the placenta is the primary mechanism of drug transfer, giving nonionized lipophilic substances easy passage and making less lipid soluble ionized substances more difficult to cross. Drug strongly bound to protein or large molecular weight drugs (e.g., heparin and insulin) do not cross the placenta. Both the immature fetal liver and placenta can metabolize drugs. Fetal drug accumulation can be problematic secondary to limited metabolic enzymatic activity along with the concern that approximately half of the blood flow from the umbilical vein bypasses the fetal liver and goes to the cardiac and cerebral circulations. Another mechanism that can also lead to prolonged effects of drugs in the fetal compartment is ion trapping. This phenomenon occurs because the fetal plasma pH is more acidic than the maternal plasma, causing weak bases (e.g., nonionized and lipophilic substances) to diffuse across the placental barrier and become ionized in the more acidic fetal blood. The net effect is the movement of drugs from the maternal to fetal compartment. This equilibrium between the maternal-fetal compartment becomes important when therapeutic fetal drug concentrations are desired (e.g., digoxin therapy for intrauterine fetal arrhythmias). Drugs are eliminated by the fetus primarily through diffusion back to the maternal compartment. As the fetal kidney matures, metabolites of drugs are excreted into the amniotic fluid [29-31].

So, during pregnancy, the following important changes can be observed:

- increase in the amount of fluid in the body,
- increase in blood volume,
- increase in plasma volume (up to 40-50%),
- increase in the volume of API distribution,
- acceleration of renal blood flow,
- impairment of intestine motility,
- impairment of liver enzymes values,
- reduction in the amount of albumin in the plasma,
- reduction in plasma pH [25].

As a result, these changes can increase API concentrations or their active metabolites and dose-dependently increase their teratogenic potential.

Scientific reports indicate that 2-5% of congenital malformations are due to the teratogenic effect of drugs, and the risk of teratogenesis or fetotoxicity of drugs largely depends on the pregnancy period [24-26,30-32].

During intrauterine development, a child goes through several important periods, which, according to the principles of their identification, can have different terms and duration. For example, it is clear and convenient to divide pregnancy into trimesters. Thus, the first, second and third trimesters are distinguished, each lasting three months (90 days, approximately 13 weeks, figure 1).

The second approach divides pregnancy into periods according to the stages of intrauterine development of a child: pre-embryo, embryo and fetus. It is essential to understand the particular changes that occur in different periods (figure 1). When using this approach, three periods are also distinguished:

- *fetus first period*, pre-embryonic, which lasts after fertilization during the first week of

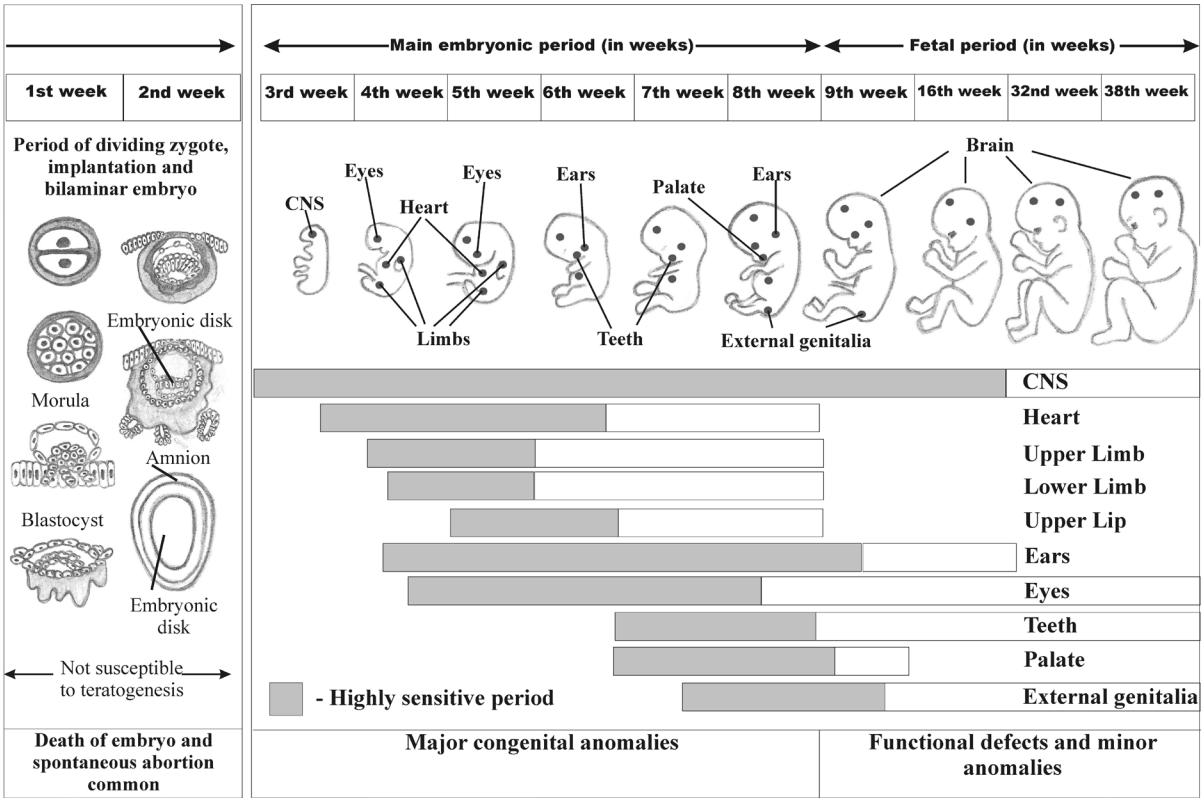

Figure 1. Critical susceptible to teratogenic impacts periods for embryo and fetus organ development [Modifyed from Moore KL, Persaud TVN, Torchia MG. Embryologie. Entwicklungsstadien – Frühentwicklung – Organogenese – Klinik, 6. Auflage. München: Urban & Fischer Verlag/Elsevier GmbH; 2013]

pregnancy. The critical moments of this period are fertilization and implantation. During this period, the exposure to negative factors causes an embryotoxic effect or the absence of any effect, the "all-or-none" law;

- *the second period* is embryonic, lasting from the third to the eighth week after fertilization (the period of organogenesis). It is the most sensitive and dangerous period (critical) for aggressive environmental factor exposure. Clusters of stem cells form the foundations for each organ's development, and these processes are susceptible to the damaging effects of internal genetic factors and external aggressive environmental influences. During this period, the influence of negative factors causes a teratogenic effect. In the period of organogenesis, especially in the third-fourth week of embryogenesis, the most significant number of congenital developmental anomalies develop;
- *the third (fetal) period* lasts from the ninth week of pregnancy until the child's birth. During this period, tissues and organs mature, and the body grows rapidly. Usually, a few malformations develop, but deformations and fractures may occur. In addition, there may be harmful impacts on the central nervous system in the form of behavioral disorders, learning disabilities and reduced intelligence [24].

According to the second approach, it becomes clear that the first three months from the moment of fertilization, the formation of the blastocyst, its implantation in the uterine wall, gastrulation and organogenesis are the most responsible. Manifestations of abnormal embryogenesis are fetal death, malformations, growth delay and functional disorders in fetus/newborn. During the last three months of pregnancy, significant risks include breathing difficulties in the newborn baby. Some drugs may also

affect labour, causing it to be premature, delayed, or prolonged. It means that the last month of pregnancy is critical too. However, this view is controversial, because a child from the 37th gestation week is already considered full-term and ready for independent life [24,26,27,33,34].

The mechanisms of the drug affecting embryo/fetus formation and growth are not always clear. It was established that they are similar to the ways of development of other types of drugs adverse reactions and are mostly related to the main pharmacological properties. The most important mechanism is considered to be a violation of catabolic processes, first of all, the synthesis of DNA and proteins. Other mechanisms include:

1. Direct toxic damage and destruction of cells or increased formation of reactive oxygen species.
2. Violation of energy exchange.
3. Inhibition of enzyme activity.
4. Increase of the excitability of the uterus, stimulation of its contractile activity.

Folate antagonism, neural crest cell disruption, endocrine disruption, oxidative stress, vascular disruption, and specific receptor- or enzyme-mediated teratogenesis could be added [35-39].

Given the consequences that may be caused by taking a medicinal product, evaluating the reasonability of its use, choosing a particular medicine, dosage form, route and course of administration are very responsible steps both for a doctor and for a pharmacist when a patient prefers self-medication.

For a pharmacist, when dispensing an OTC drug to a pregnant woman, the primary source of information is a leaflet or instruction for medical use or information for the patient or drug label; in other words, the information that is officially approved by the state agencies or departments of the relevant country (Food and Drug Administration in the USA, Office for Registration of Medicinal Products, Medical Devices and Biocidal Products in Poland, State Expert Center in Ukraine, EMA in Europe etc.) [40].

The corresponding document must contain the chapter "Pregnancy and lactation", which sets out the arrangements (permission/restriction/warning/prohibition) for medicinal product use. In different countries, particular methods are used to present this information per the adopted approaches and classifications [40].

For example, until 2015, the FDA used the classification of the drug teratogenicity degree based on the preclinical and clinical experience of API use and was denoted by Latin letters. Since 2015, new requirements for labeling the risk of teratogenicity have been applied. The final rule requires the removal of the pregnancy categories A, B, C, D, and X from all human prescription drug and biological product labeling and demands that the labeling include a summary of the risks of using a drug during pregnancy and lactation, a discussion of the data supporting that summary, and relevant information to help health care providers make prescribing decisions and counsel women about the use of drugs during pregnancy and lactation [40].

Pharmaceutical care in obstetrics and perinatology includes a comprehensive program of cooperation between specialists in obstetrics, gynecology, neonatology, a pharmacist and a pregnant woman, which covers the entire period of drug therapy, starting from the moment of prescription/recommendation and dispensing of drugs until the end of their impact.

The most important task of a pharmacist/clinical pharmacist is to ensure the effective and safe use of medicines, including over-the-counter ones [2,17].

A pharmacist must adhere to certain principles when providing information support and counseling assistance to a pregnant woman. Communication should begin with finding out the symptom (feeling of being unwell) that bothers the pregnant woman, how long it lasts, the presence of aggravating factors that exclude the possibility of independent use of over-the-counter medicines and finding out the factors that can contribute to the disorder development.

In case of the absence of threatening symptoms and the presence of signs of mild, functional disorder, the pharmacist's advice should primarily include recommendations for lifestyle modification and non-pharmacological approaches to the elimination and prevention of disorder. This category includes the creation of a comfortable living environment (silence, quiescency, fresh air), improvement of the regime of wakefulness and rest (dosed physical activity, walks), adherence to a specific diet (good nutrition and inclusion/exclusion of certain products in the diet), rejection of bad habits, etc. These measures aim to alleviate symptoms and allow pregnant woman to avoid taking medication for as long as possible. It should be reminded that we are talking about mild disturbances of well-being [29].

Table II. Principles of pharmaceutical care of a pregnant woman

When it concerns to choosing and taking medicine by a pregnant woman, a pharmacist must follow the same principles as a doctor:
- the benefit of drug administration should exceed the risk of adverse drug reaction development, first of all, the negative impacts on the fetus;
- when choosing a specific drug, pay attention to pharmacokinetic properties, in particular, the ability of API to penetrate the placental blood barrier;
- when choosing a specific drug, pay attention to the period of pregnancy;
- recommend a drug with the most effective and least dangerous API;
- consider the possibility of using topical dosage forms in order to minimize the API systemic absorption;
- do not recommend combined medicines, for example, the remedies for the symptomatic treatment of a cold, which can simultaneously contain an analgesic-antipyretic, a vasoconstrictor alpha-adrenomimetic, a decongestant, an antitussive, a vitamin and a respiratory analeptic;
- recommend the minimum effective dose for the shortest time. For pregnant women, it is rational to dispense one dose for one-time use, for example, an antacid in a stick or sachet to eliminate heartburn;
- long-term use of an over-the-counter medicinal product must be approved by a doctor;
- in the case of lack of effectiveness of the medicinal product or the development of undesirable reactions, urgently refer a patient to a doctor!

If it is necessary, a doctor must prescribe the drug. However, in the case of OTC drugs usage in the self-medication framework, a pregnant woman can be advised by a pharmacist (table II).

The important circumstances for the rational use of drugs by pregnant women include strict adherence to the principles of evidence-based medicine and pharmacy; achieving compliance with a pregnant woman, pharmacoeconomic justification of therapy; keeping record of all stages of pharmacotherapy, analysis of pharmacotherapy results, as well as observation, recording and assessment of remote consequences of pharmacotherapy in offspring.

Conclusions

- The problem of the rational and safe use of drugs by a pregnant woman is an important component of pharmaceutical care, especially in the case of responsible self-medication.
- When choosing a drug (including an over-the-counter drug) for a pregnant woman, it is necessary to consider numerous factors that relate to a special patient and the peculiarities of the active pharmaceutical ingredient.
- Recommendations concerning the possibility of using drugs and/or active pharmaceutical ingredients may differ in certain countries. It requires careful attention to the accompanying drug paper.
- The pharmacist/clinical pharmacist is an essential medical team member to ensure the effective and safe use of drugs by the pregnant woman, and to prevent and timely detect adverse effects.

Conflict of interest
None

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